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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,867	BAKER ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Preliminary Amendment filed 13 December 2001 has been received and entered in full.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code (pp. 304 line 5; pp. 306 line 23). See MPEP §608.01.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration (for Inventor Dan Eaton). See 37 CFR 1.52(c).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims **28-47** are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

5. The claims are directed to a nucleic acid of the SEQ ID NO: 281 polynucleotide sequence which encodes the protein of the SEQ ID NO: 282 amino acid sequence, as well as variants, derivatives, mutations, and fragments thereof. The specification discloses that the nucleic acid of the SEQ ID NO: 281 polynucleotide sequence encodes the protein of the SEQ ID NO: 282 amino acid sequence (therein notated as "PRO1780" and "DNA71169-1709"). The SEQ ID NO: 281 polynucleotide sequence encodes a protein that bears similarity to glucuronosyltransferase as well as other proteins. The glucuronosyltransferase class of protein is known in the art to be large and diverse and the Specification as filed does not identity which glucuronosyltransferase is claimed or what the properties of the claimed invention are.

6. King *et al.* (September 2000) "UDP-glucuronosyltransferases." Curr Drug Metab. **1**(2): 143-161 teaches that glucuronidation represents a major pathway which enhances the elimination of many lipophilic xenobiotics and endobiotics to more water-soluble compounds. The UDP-glucuronosyltransferase (UGT) family catalyzes the glucuronidation of the glycosyl group of a nucleotide sugar to an acceptor compound at a nucleophilic functional group of oxygen (e.g.,

hydroxyl or carboxylic acid groups), nitrogen (e.g., amines), sulfur (e.g., thiols), and carbon, with the formation of a β-D-glucuronide product (pp. 143-144). The UGTs are found in the liver, the kidney, gastrointestinal tract, and brain (Table 5). King *et al.* teaches that more than 35 different UGT genes from several different species are known and are divided into two distinct subfamilies based on sequence identities, UGT1 and UGT2. The UGT1 gene subfamily consists UGTs that result from alternate splicing of multiple first exons and share three common exons 2-5 (pp. 146-149). The UGT1 subfamily catalyze the glucuronidation of a chemicals including bilirubin, amines, and phenol (Table 4). The UGT2 gene family differs in that the UGT2 mRNAs are transcribed from distinct, individual genes (pp. 149-153). The UGT2 subfamily catalyze the glucuronidation of a diverse chemicals including steroids, bile acids, and opioids (Table 4).

7. The instant specification does not disclose any data for the any activity of the protein of the SEQ ID NO: 282 amino acid sequence. There are no well-established utilities for newly discovered biological molecules. Applicant asserts numerous uses and includes a number of assays. However, the specification contains several assertions of utilities. For purposes of expedited examination, the Examiner will address only assays and uses directly applicable to polynucleotide of the SEQ ID NO: 281 nucleic acid sequence (therein notated as "PRO1780" and "DNA71169-1709"). Each of the relevant asserted utilities will be discussed in turn.

a. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence encodes a glucuronosyltransferase protein of the polypeptide sequence of SEQ ID NO: 282:* The specification's assertion that the nucleic acid molecule of the SEQ ID NO: 281 polynucleotide sequence encodes a glucuronosyltransferase protein of the polypeptide sequence of the SEQ ID NO: 282 amino acid sequence is not substantial. This assertion is

based on sharing sequence homology with a least one known glucuronosyltransferase protein. [see Barbier *et al.* (1999) "Cloning and characterization of a simian UDP-glucuronosyltransferase enzyme UGT2B20, a novel C19 steroid-conjugating protein." Biochem. J. **337**: 567-574 teaches an UGT sequence that shares 24.3% sequence homology with SEQ ID NO: 282 (Figure 1; Table 1)]. However, this assertion is not substantial as the sequence of glucuronosyltransferases are diverse nor is it specific as their tissue distribution is greatly varied. Strassburg *et al.* (17 November 2000) "Polymorphic gene regulation and interindividual variation of UDP-glucuronosyltransferase activity in human small intestine." J Biol Chem. **275**(46): 36164-71 teaches that the catalytic activity and substrate specificity varied in UGTs expressed in the duodenum, jejunum, and ileum (Figure 3). UGT specificity activity for 1-naphthol, 4-MU, 4-ni-trophenol, and HDCA was greater in liver than in the intestinal samples. But a greater number of compounds were glucuronidated at higher rates in small intestine. including 2-hydroxy estrone, β-estradiol, estrone, PhIP, 7-hydroxy benzo(a)pyrene, and 2-hydroxyamino-1-methyl-6-phenylimidazo-(4,5-β)-pyridine, imipramine, and amitriptyline (Figure 3). The UGTs also varied in their expression patterns. Using DRT-PCR, the regulation of the UGT1A locus as well as the UGT2B4, UGT2B7, UGT2B10, and UGT2B15 genes was analyzed in 18 tissue samples from duodenum, jejunum, and ileum. A pattern of tissue-specific gene expression was observed in small intestine, which exhibited considerable differences from that found in liver and colon (Table II and Figure 1). Liver (UGT1A1, UGT1A3, UGT1A4, UGT1A6, and UGT1A9) and colon (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, and UGT1A10) tissue have been

characterized to express specific UGT1A transcript patterns without variation (Table II and Figure 2). In intestine, gene expression included UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A10, UGT2B4, UGT2B7, and UGT2B15 transcripts, and the absence of UGT1A5, UGT1A7, UGT1A8, and UGT1A9, and most UGT2B10 transcripts. As an example, the UGT1A6 gene was expressed in fewer jejunum samples, UGT2B4 mRNA was expressed more often in the ileum, and UGT2B7 transcripts were expressed more often in the jejunum. Therefore, the specification's assertion that the nucleic acid molecule of the SEQ ID NO: 281 polynucleotide sequence encodes a glucuronosyltransferase protein of the polypeptide sequence of the SEQ ID NO: 282 sequence is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what its properties are. Nor is the assertion specific, as teaches the wide sequence variance and diverse tissue distribution of glucuronosyltransferases. For instance, Beaulieu et al. (9 July 1998) "Isolation and characterization of a human orphan UDP-glucuronosyltransferase, UGT2B11." Biochem Biophys Res Commun. **248**(1): 44-50 teaches that human UGT enzymes are classified into two families (UGT1 and UGT2) which are further divided into subfamilies regarding sequence homology (Figure 1; Table 1). The UGT1 gene locus contains the necessary exons for 12 UGT1 transcripts including three pseudogenes. From cDNA sequence and examination of the gene locus, each UGT1 gene is composed of a unique first exon and four common exons 2 to 5. The UGT2 family is divided into two subfamilies, UGT2A and UGT2B, where the latter subfamily comprises enzymes conjugating bile salts and steroid hormones. Comparison of the UGT2B cDNA sequences and FISH analysis

suggests that these isoenzymes are encoded by independent genes resulting from duplication events of a common ancestral gene. In humans, eight cDNAs from the UGT2B subfamily have been isolated including three variants. Extensive tissue distribution of the human and monkey UGT2B isoenzymes has demonstrated that these enzymes are expressed in the liver as well as in a large number of extrahepatic tissues (Figure 3). From these cDNAs, UGT2B4 and UGT2B7 are known to be implicated in the conjugation of bile acids, catecholestrogens and phenolic derivatives. UGT2B7, UGT2B15 and UGT2B17 are mainly involved in the conjugation of steroid hormones especially androgens and their metabolites. On the other hand, UGT2B10 cDNA transfected in COS-7 cells exhibited no activity with over forty potential substrates tested (Table 2). Therefore a single glucuronosyltransferase gene locus may give rise to numerous isozymes which while similar in sequence varies in tissue and substrate specificity. In addition, function cannot be adequately predicted based solely on structural similarity to a protein found in the sequence databases. Thus one must be cautious in their use of sequence homology to assign a structure and function to a protein on sequence alone. For instance, Erps et al. (February 1994) "Identification of two single base substitutions in the UGT1 gene locus which abolish bilirubin uridine diphosphate glucuronosyltransferase activity in vitro." J Clin Invest. **93**(2): 564-70 teaches that a single base substitution in the UGT1, serine to phenylalanine at codon 376 and glycine to glutamic acid at codon 309, abolishes its activity. Mutant UGT1 cDNAs were constructed by site-directed mutagenesis, inserted into expression vectors, and transfected into COS-1 cells (Figure 4). Only wild-type UGT1 clones supported the synthesis of the bilirubin

transferase protein and not the mutants (Figure 5). Therefore, even point mutations at positions glycine 309 and serine 376 can abolish a glucuronosyltransferase's activity. Sequence homology is not a reliable as the sole basis upon which to establish biological activity. For example, Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39 state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400 states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250 who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223 remarks that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (April 1999) "Errors in genome annotation." Trends in

Genetics **15**(4): 132-133 argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427 add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. In any case, the art clearly shows that structural similarity of different glucuronosyltransferase proteins is not predictive of expression patterns or functional similarity. Thus the specification's assertion that the polypeptide of the SEQ ID NO: 282 amino acid sequence encoded by the nucleic acid of the SEQ ID NO: 281 polynucleotide sequence has glucuronosyltransferase activity is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what those activities are. Therefore this utility is neither specific nor substantial.

b. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used as probe or primer:* This asserted utility is not specific or substantial. The specification asserts that the claimed isolated nucleic acid, variants, and fragments thereof are useful as probes to detect genes encoding the nucleic acid of the polynucleotide sequence of SEQ ID NO: 282, as primers or hybridization probes in screening libraries, to amplify corresponding gene fragments, to identify potential genetic

disorders, in sequence arrays, to screen collections of genetic material from patients who have a particular medical condition, in restriction fragment length polymorphism (RFLP) screens, to screen a human genomic library using PCR and other methods, to search sequence databases, and to identify mutations associated with a particular disease. Since there is no substantial utility for the encoded polypeptide (the SEQ ID NO: 282 amino acid sequence), there is also no substantial utility for the nucleic acid probes to identify such or the claimed nucleic acids. Iwano *et al.* (1 August 1997) "A critical amino acid residue, asp446, in UDP-glucuronosyltransferase." Biochem J. **325**(Pt 3): 587-91 teaches that a single amino acid residue, Asp446, is essential for the enzymic activity of UDP-glucuronosyltransferase (UGT). A mutant gluconosyltransferase (D446G) did not show any activity at all (Tables 1 & 2). Asp446 was conserved in all UGTs and UDP-galactose:ceramide galactosyltransferases reported, suggesting that Asp446 plays a critical role in each enzyme. Thus it is plausible to use polynucleotides as probes and primers when a real-world utility when the target gene's identity, function, and relevant mutations thereof are known. But in the instant case, it would take significant further research to determine if the polynucleotide could be used as probes for any particular disease, mutation, or condition, since no nexus between any disease or condition and an alteration or mutation in the nucleic acid of the SEQ ID NO: 281 polynucleotide sequence expression levels or form (i.e. mutations) has been disclosed in the specification. Further, since all nucleic acids can be used as probes or primers, this asserted utility is not specific.

c. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used to make inhibitory antisense or sense oligonucleotides:* This asserted utility would only be specific and substantial if the encoded polypeptide (the SEQ ID NO: 282 amino acid sequence) had a specific and substantial utility. This utility is not specific as any nucleic acid can be used to make inhibitory antisense or sense oligonucleotides. Otherwise, significant further research would be required of the skilled artisan to use the claimed nucleic acid to make antisense or sense oligonucleotides, since it is unclear when it would be desirable to use the inhibitory antisense or double stranded oligonucleotides.

d. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used in chromosome mapping:* This asserted utility is not specific or substantial. In order to be useful as a chromosomal probe, the precise chromosomal map position must be disclosed. For example, Riedy *et al.* (April 2000) "Genomic organization of the UGT2b gene cluster on human chromosome 4q13." Pharmacogenetics **10**(3): 251-60 teaches that the genomic characterization and chromosomal localization of three UGT2B genes [UDP-glucuronosyltransferases (UGTs)] comprise a large cluster of related sequences, including pseudogenes found on human chromosome 4q13 (Figures 1 & 2). A genomic map spanning approximately 500-1000 kb of this region reveals the presence of three previously described UGT2B genes, at least two previously uncharacterized pseudogenes, and a significant number of remnant gene fragments (Figure 3). Riedy *et al.* noted in view of the large number of specific genes, degree of allelic diversity their data suggest a recent evolutionary history of gene duplication, mutation and rearrangement. The instant Specification does not teach the chromosome location of the nucleic acid of

the SEQ ID NO: 281 polynucleotide sequence. Hence the skilled artisan is confronted with using an uncharacterized sequence in chromosome mapping of a large and complex gene superfamily. Although there is increased expression of this gene in three lung tumor lines (LT4, LT7, and LT22), no mutations were found (Table 8). To the contrary, in the instant Specification not chromosome location or specific disease state has been ascribed to the nucleic acid of the SEQ ID NO: 281 polynucleotide sequence which encodes the polypeptide of the SEQ ID NO: 282 amino acid sequence thus failing to support the asserted identity of the protein encoded by the SEQ ID NO: 281 polynucleotide sequence. In view of the art, Sen (January 2000) "Aneuploidy and cancer." Curr Opin Oncol. **12**(1): 82-88 teaches that chromosome aberrations known as aneuploidy are commonly observed in tumors. Whether aneuploidy is a cause or consequence of the tumor is unclear. While widespread in human tumors, the cancer cells show great phenotypic diversity in morphology, proliferation, antigen expression, drug sensitivity, and metastasis (pp. 82). Accordingly, gene copy number may be due to abnormal chromosome number, duplication, or fragmentation therefore not indicative of particular relevance to the genes encoded therein. Also, gene copy number does not predictably influence protein levels. In the instant application, the absence of follow-up experiments explaining the expression of the instant nucleic acid in the three cell lines (LT4, LT7, and LT22). Many tumor cells are aneuploid thus most have multiple chromosomes. Therefore substantial further research by the skilled artisan is required to determine where this particular sequence is mapped in order to use the nucleic acid in the asserted utility as a chromosomal map

probe or to detect tumors. The asserted utility is also not specific, since the entire class of genes can be asserted to be used in this way.

e. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used to make polypeptides for analysis of binding and/or interacting molecules:* This asserted utility not specific or substantial. The instant specification does not disclose any known function for the claimed nucleic acid (the SEQ ID NO: 281 polynucleotide sequence, the polypeptide encoded therein (the SEQ ID NO: 282 amino acid sequence) nor any disease state, toxin, or poison associated either. Therefore, it is not clear how the skilled artisan would use a polypeptide manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required to determine how to use the claimed nucleic acid, the asserted utility is not substantial. In addition, this utility assertion is not specific as it can be applied to any given nucleic acid.

f. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used in gene therapy methods:* This asserted utility is not specific or substantial. This utility is not specific as any nucleic acid can be used in such a manner. The instant specification does not disclose any known disease state, toxin, or poison associated with the nucleic acid of the SEQ ID NO: 281 polynucleotide sequence. For example, Mackenzie *et al.* (September 2000) "Polymorphisms in UDP glucuronosyltransferase genes: functional consequences and clinical relevance." Clin Chem Lab Med. **38**(9): 889-892 teaches that polymorphic variations in the UDP glucuronosyltransferases (UGT) have a significant impact on detoxification and elimination of drugs and toxins. Twenty-four human UGT genes have been identified but polymorphisms were reported in only

five UGTs: UGT1A1, UGT1A6, UGT2B4, UGT2B7 and UGT2B15 (Figure 1). Polymorphisms in UGT1A1, the major bilirubin-glucuronidating form, result in a decreased capacity to glucuronidate bilirubin, such as observed in Gilbert Syndrome and some forms of perinatal jaundice. The frequencies of individual UGT1A1 polymorphisms show extensive variability across ethnic groups. Two variants of UGT1A6 and UGT2B4 and one variant of UGT2B7 and UGT2B15 have been identified. However, the clinical significance of these variants is unclear. More UGT polymorphisms will undoubtedly be discovered when the human genome is sequenced. However, unless the UGT in question is responsible for the exclusive metabolism of a particular drug or chemical (e.g. UGT1A1 and bilirubin) or is the predominant or only UGT present in the cell, it is unlikely that these polymorphisms will be of major clinical significance (pp. 891). Therefore, it is not clear how the skilled artisan would use the gene therapy constructs made with the claimed nucleic acid for therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

g. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be expressed in cell lines:* This asserted utility is not specific or substantial. The specification asserts that the claimed nucleic acid is useful for expression in cell lines. Since there is no substantial utility for the claimed nucleic acid or the encoded polypeptide therein, there is also no substantial utility for the transformed cell lines. It would take significant further research to determine if the transformed cells could be used for particular purpose, since no nexus between a disease state, mutations, expression

patterns, signaling pathways, and the nucleic acid of SEQ ID NO: 281 polynucleotide sequence have been disclosed in the specification. Further, since all nucleic acids can be used to transform cell lines, this asserted utility is not specific.

h. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used to make chimeric proteins:* This asserted utility is neither specific nor substantial. The instant specification does not disclose any known a disease state, mutations, expression patterns, activity, or signaling pathways associated with the nucleic acid of SEQ ID NO: 281 polynucleotide sequence. Therefore, it is not clear how the skilled artisan would use a chimeric polypeptide for therapeutic, diagnostic, or research uses. Since significant further research would be required to determine how to use the claimed chimeric polypeptide, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

i. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used in tissue typing:* This asserted utility is not specific or substantial. The specification discloses that primary lung tumor cells expressed "elevated" levels of the nucleic acid of SEQ ID NO: 281 polynucleotide sequence. This expression level is not clearly defined in a clinical, biochemical, or diagnostic context and therefore is of dubious value. In view of the art, Strassburg *et al.* (August 1997) "Differential expression of the UGT1A locus in human liver, biliary, and gastric tissue: identification of UGT1A7 and UGT1A10 transcripts in extrahepatic tissue." Mol Pharmacol. **52**(2): 212-220 teaches the differential expression of the UGT1A locus in human hepatic and extrahepatic tissues despite high levels of sequence identity between the UGT transcripts (Figure 1). Sequence identity

between the first exons of the cluster encoding UGT1A3, UGT1A4, and UGT1A5 and the cluster encoding UGT1A7, UGT1A8, UGT1A9, and UGT1A10 is approximately 93%. DRT-PCR analysis of 16 human hepatocellular, four biliary, and two gastric tissue samples demonstrated patterns of expression that were unique for each tissue (Figure 6). The expression of UGT1A1, UGT1A3, UGT1A4, and UGT1A6 was observed in both hepatocellular and biliary tissues, although the over-all expression levels were lower in biliary tissue. Gastric tissue was characterized by the expression of UGT1A3 and UGT1A6 but not UGT1A1 and UGT1A4. Transcripts encoding UGT1A5 and UGT1A8 were absent in all three tissue types. Significantly, the hepatocellular expression of the UGT1A locus was characterized by the unique expression of UGT1A9. This particular form was not expressed in either biliary or gastric tissue. In contrast, gastric epithelium was characterized by the unique expression of UGT1A7, which was not detected in hepatocellular or biliary tissue. Additionally, the expression of UGT1A10 was specifically localized to both of the nonhepatocellular tissues. Strassburg *et al.* provide evidence for complex and tissue-specific regulation underlying human UGT1A control. Thus this asserted utility is not substantial because a skilled artisan would be confronted by an undue experimentation burden to discern what tissues specifically express the claimed nucleic acid and what the relevance is. Nor is neither it specific because the identity of the type of lung cancer has not been identified nor the nucleic acid of the SEQ ID NO: 281 polynucleotide's role therein.

j. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used in drug development (such as agonists and antagonists):* This asserted utility is not

specific or substantial. In such methods, compounds are screened either physically or through computer modeling to determine their ability to bind to the target sequence. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in the SEQ ID NO: 281 polynucleotide sequence expression levels or forms (i.e., mutations). Therefore, in light of the absence of a clearly defined isoform and its ligand/metabolite/inhibitor properties, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid can be used in such a manner.

k. *The isolated nucleic acid of the SEQ ID NO: 281 polynucleotide sequence can be used in making transgenic animals:* This asserted utility is not specific or substantial. No phenotype has been disclosed for such transgenic animals. In the absence of such disclosure, the skilled artisan would have to experiment significantly in order to determine how the transgenic animals could be used. Therefore, the asserted utility is not substantial. Also, any nucleic acid can be used in this manner therefore the asserted utility is not specific either.

8. Therefore, in the absence of a well-established utility, and the absence of a specific, substantial and credible asserted utility, the claimed invention lacks patentable utility under 35 U.S.C. § 101.

9. Claims **28-47** are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Furthermore, claims **28-47** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

11. The claims are drawn very broadly to an isolated nucleic acid comprising the SEQ ID NO: 281 nucleic acid sequence, variants, derivatives, and fragments thereof. The language of said claims encompasses sequence variants, fragments, and derivatives thereof.

12. The specification teaches that the nucleic acid of the SEQ ID NO: 281 polynucleotide sequence encodes the polypeptide of the SEQ ID NO: 282 amino acid sequence (therein notated as "PRO1780" and "DNA71169-1709").

13. A person skilled in the art would recognize that predicting the efficacy of using sequence homology alone to predict the structure, nature, and function of the polynucleotide of the SEQ ID NO: 281 nucleic acid sequence, variants, derivatives, and fragments thereof as highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of producing, isolating, and characterizing the polynucleotide of the SEQ ID NO: 281 nucleic acid sequence, variants, derivatives, and fragments thereof, such a disclosure would not be considered enabling since the state of protein biochemistry is highly

unpredictable and complex. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) THE BREADTH OF THE CLAIMS;
(B) THE NATURE OF THE INVENTION;
(C) THE STATE OF THE PRIOR ART;
(D) THE LEVEL OF ONE OF ORDINARY SKILL;
(E) THE LEVEL OF PREDICTABILITY IN THE ART;
(F) THE AMOUNT OF DIRECTION PROVIDED BY THE INVENTOR;
(G) THE EXISTENCE OF WORKING EXAMPLES; AND
(H) THE QUANTITY OF EXPERIMENTATION NEEDED TO MAKE OR USE THE INVENTION BASED ON THE CONTENT OF THE DISCLOSURE.

14. The following references are cited herein to illustrate the state of the art of protein biochemistry.

15. On the breadth of the claims, Owens & Ritter (1995) "Gene structure at the human UGT1 locus creates diversity in isozyme structure, substrate specificity, and regulation." Prog Nucleic Acid Res Mol Biol. **51**: 305-38 teaches that UGTs vary in their sequence, structure, and substrate specificity. The UGT1 locus encodes at least 9 splice variants (Figure 2). These isoforms are any share as low as 58% and as high at 95% nucleic acid sequence homology (Table II). Thus as the claims as instantly presented do not specify which glucuronosyltransferase is instantly claimed, nor what is its activity, and in view of Owens & Ritter a large number of potential identities are possible. Furthermore Ouzzine *et al.* (9 July 1999) "Expression of a functionally active human hepatic UDP-glucuronosyltransferase (UGT1A6) lacking the N-terminal signal sequence in the endoplasmic reticulum." FEBS Lett. **454**(3): 187-91 teaches that UDP-glucuronosyltransferase 1A6 (UGT1A6) is expressed as a precursor with an N-terminal cleavable signal peptide. The

deletion of the signal peptide sequence does not interrupt membrane targeting or integration when expressed in an *in vitro* transcription-translation system, as shown by N-glycosylation, resistance to alkaline treatment and protease protection (Figure 1). Furthermore, UGT1A6 lacking the signal peptide (UGT1A6Δsp) was targeted to the endoplasmic reticulum in mammalian cells as shown by immunofluorescence microscopy and was catalytically active with kinetic constants for 4-methylumbelliferone glucuronidation similar to that of the wild-type (Figure 2). Thus in the absence of such guidance and/or examples in the Specification, the skilled artisan is left to experiment to determine what is considered to be the signal peptide of the SEQ ID NO: 282 polypeptide as encoded by the polynucleotide of the SEQ ID NO: 281 nucleic acid.

16. On the nature of the invention, Arnold *et al.* (7 March 2000) "Two homologues encoding human UDP-glucose:glycoprotein glucosyltransferase differ in mRNA expression and enzymatic activity." Biochemistry **39**(9): 2149-63 teaches two cDNAs encoding human UDP-glucose:glycoprotein glucosyltransferase (UGT) homologues. HUGT1 which encodes a 1555 amino acid polypeptide and HUGT2 encodes a 1516 amino acid polypeptide. HUGT1 shares 55% identity with HUGT2 and 31-45% identity with *Drosophila, Caenorhabditis elegans,* and *Schizosaccharomyces pombe* homologues HUGT1 is expressed as multiple mRNA species that are induced to similar extents upon disruption of protein folding in the endoplasmic reticulum (Figures 1 & 2). In contrast, HUGT2 is transcribed as a single mRNA species that is not induced under similar conditions (Figure 4). HUGT1 and HUGT2 mRNAs are broadly expressed in multiple tissues and differ slightly in their tissue distribution (Figure 3). Extracts from HUGT1-transfected cells displayed a 27-fold increase in the transfer of [(14)C]glucose from UDP-[(14)C]glucose to denatured substrates (Figures 6 & 7). Despite its high degree of sequence

identity with HUGT1, the expressed recombinant HUGT2 protein was not functional under the conditions optimized for HUGT1. In contrast, no such guidance is present in the instant Specification. Thus the skilled artisan is left to experiment and determine what is required and which residues are required for function of the instantly claimed nucleic acid.

17. On the existence of working examples, Jedlitschky *et al.* (15 June 1999) "Cloning and characterization of a novel human olfactory UDP-glucuronosyltransferase." Biochem J. **340**(Pt 3):837-43 teaches the molecular cloning and functional characterization of a human olfactory UDP-glucuronosyltransferase (UGT) (Figure 1). The cloned protein is composed of 527 amino acids with an identity of 87% with a rat olfactory UGT and of 43-62% with other human UGT isoforms (hUGT2A1) (Figure 2). The gene was mapped to chromosome 4q13 by fluorescence in situ hybridization (Figure 3). The expression appeared to be specific for the olfactory tissue. This UGT isoform showed a broad substrate spectrum including a range of phenolic compounds as well as aliphatic and monoterpenoid alcohols, among them many odorants (Table 2). Therefore one could isolate and clone a UGT using sequence homology as a guide but it is only the beginning of the characterization stage of the invention. In contrast, none such work has been done to characterize and explain how to use the instantly claimed nucleic acid.

18. Regarding derivatives and fragments of isolated nucleic acid comprising the SEQ ID NO: 281 polynucleotide sequence, variants, derivatives, and fragments thereof and the polypeptides encoded therein, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid

substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. For example, Bosma *et al.* (July 1993) "A mutation in bilirubin uridine 5'-diphosphate-glucuronosyltransferase isoform 1 causing Crigler-Najjar syndrome type II." Gastroenterology **105**(1): 216-20 teaches that a single nucleotide shift in an UGT gene can lead to inherited unconjugated hyperbilirubinemia in Crigler-Najjar type II (CN II) (pp. 216). Both B-UGT isoenzymes (B-UGT1 and B-UGT2) were identified in humans are derived from a single gene by alternative splicing. CN II patients were found to be homozygous for a nucleotide shift in the unique region of B-UGT1, changing a arginine into a tryptophan, and also for a nucleotide shift in the unique region of B-UGT2, changing a leucine into a valine. Analysis of other family members and of 50 control subjects showed that the mutation in B-UGT1 causes CN II, whereas the mutation in B-UGT2 is a polymorphism (Figure 3). Furthermore, these or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 433-506]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of

changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the

unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

19. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *sequence homology predictions* to the actual structure, function, and nature of the polynucleotide of the SEQ ID NO: 281 nucleic acid sequence, variants, derivatives, and fragments thereof as exemplified in the references herein.

20. Claims **28-47** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not contain a written description of variants and fragments of the claimed nucleic acid.

21. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

22. With the exception of the polynucleotide of the SEQ ID NO: 281 nucleic acid sequence, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

23. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

24. Therefore, only isolated polypeptides comprising the *polynucleotide* sequence set forth in SEQ ID NO: 281, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

25. Claims **28-47** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

26. The invention appears to employ novel nucleic acid (the cDNA deposited under ATCC accession number 203467). Since the nucleic acid is essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public.

27. The specification does not disclose a repeatable process to obtain the cDNA deposited under ATCC accession number 203467 and it is not apparent if the cDNA deposited under ATCC accession number 203467 is readily available to the public. If the cDNA deposited under ATCC accession number 203467 is not so obtainable or available, the requirements of 35 U.S.C. §112 may be satisfied by a deposit of the cDNA deposited under ATCC accession number 203467.

28. It is noted that Applicant has deposited the cDNA deposited under ATCC accession number 203467 (pp. 517-519 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cDNA molecules have been deposited under the Budapest Treaty and that the cDNA deposited under ATCC accession number 203467 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

29. Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include such, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information.

30. Claims **28-33, 35-37,** and **41** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

31. The claims recite "the extracellular domain" (e.g. claim 28, part c). The Specification does not clearly indicated where the extracellular domain is. See Figures 159 & 160, which indicates the presence of several punative transmembrane domains thus implying several extracellular domains.

32. Also the claims recite "the extracellular domain lacking its associated signal peptide". The art recognizes that full-length, secreted proteins often have signal peptides that are cleaved during processing. However, such signal peptides are not known to be associated with "domains" of a full-length protein such as an extracellular domain.

33. Claims **41-43** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

34. The term "stringency" in claim 42 is a relative term which renders the claim indefinite. The term "stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

35. To satisfy the requirements of 35 U.S.C. §112 ¶2 Applicant must unambiguously define the limitations of the claims. "Stringent conditions" for hybridization, while known the art, are not unambiguously defined. A great deal of latitude and a range of conditions may be construed as "stringent". Also, stringency may be low, moderate, or high, none of which is specified by the claims as instantly neither presented nor supported by the Specification. For instance, the Roche website defines hybridization conditions under four parameters: temperature, pH, concentration

of monovalent cations, and the presence of organic solvents, none of which are defined by the claims or the Specification ("Nucleic Acid Hybridization- General Aspects" pp. 33-37 Roche website retrieved on 12 May 2004). Also the NIH Division of Intramural Research teaches that "Nucleic Acid Hybridization" conditions vary. For temperature it teaches that it may be 25oC below duplex melting temperature, which varies due to the length of the polynucleotide and the GC content. Also, salt concentrations may vary between 5 to 6x SCC and denaturing agents such a formamide ranges from 1% to 50% (NIH Division of Intramural Research "Nucleic Acid Hybridization" retrieved from NIH website on 12 May 2004).

36. Futhermore Umansky *et al.* US 6,287,820 states:

> Numerous equivalent conditions can be employed to comprise either low or high stringency conditions; factors such as the length and nature (DNA, RNA, base composition) of the probe and nature of the target (DNA, RNA, base composition, present in solution or immobilized, etc.) and the concentration of the salts and other components (e.g., the presence or absence of formamide, dextran sulfate, polyethylene glycol) are considered and the hybridization solution can be varied to generate conditions of either low or high stringency hybridization different from, but equivalent to, the above listed conditions. The term "hybridization" as used herein includes "any process by which a strand of nucleic acid joins with a complementary strand through base pairing".
>
> "Stringency " typically occurs in a range from about Tm-5°C. (5°C below the T_m of the probe) to about 20°C to 25°C below T_m. As will be understood by those of skill in the art, a stringent hybridization can be used to identify or detect identical polynucleotide sequences or to identify or detect similar or related polynucleotide sequences.

37. Therefore, stringent hybridization can be used to detect similar or related polynucleotide sequences, but there is no definite limit as to how similar or related the polynucleotide sequences have to be, and the claims are indefinite.

38. Therefore the skilled artisan is not apprised of the metes and bounds of what constitutes "stringent conditions". Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined. Incorporation of those conditions

which Applicant feels defines the term "stringent conditions" into the claims would obviate the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

39. Claims **28-39** and **41-47** are rejected under 35 U.S.C. 102(a) as being anticipated by WO 00/77239 (McCarthy *et al.*) 21 December 2000.

40. WO 00/77239 teaches a polypeptide that shares 100% sequence identity with the polypeptide of the SEQ ID NO: 282 amino acid sequence and nucleic acids thereof including nucleic acids and polypeptides with extracellular domain(s) and/or signal domain(s) thus meeting the limitations of claims 28-39 (pp. 2-3, 5, 16-17; Claim 8; Figures 1-3).

41. WO 00/77239 teaches nucleic acids that hybridize, including under stringent conditions, to said nucleic acid thus meeting the limitations of claims 41-43 (pp. 80; 83).

42. WO 00/77239 teaches a vector operably linked to said nucleic acid and host cells including *E. coli* and yeast cells thus meeting the limitations of claims 44-47 (pp. 5; 107-108).

Summary

43. No Claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

CJN
July 8, 2004

LORRAINE SPECTOR
PRIMARY EXAMINER